8-17-05

PATENT
Docket No. A-68668/RFT/TAL/TAW
Dorsey File No. 465174-00312

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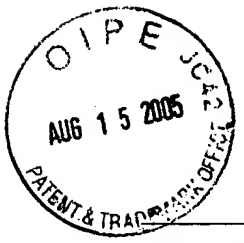

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Group No.: 1642
ALLISON, *et al.*	Examiner: Rawlings, S. L.
Serial No.: 09/454,481	Confirmation No.: 3796
Filing Date: December 3, 1999	"EXPRESS MAIL" LABEL NO.: EV 695792140 US
For: STIMULATION OF T CELLS AGAINST SELF ANTIGENS USING CTLA-4 BLOCKING AGENTS	DATE OF DEPOSIT: AUGUST 15, 2005

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APPELLANT'S BRIEF

Sir:

This appeal brief, filed in triplicate in connection with the above-captioned patent application, and is in response to the final Office Action mailed October 8, 2004. This appeal is taken pursuant to Rule 41.37, following the Notice of Appeal filed January 10, 2005, and received by the Patent Office on January 14, 2005, along with the requisite fee set forth in 37 CFR § 1.17(c). This appeal is being filed on August 15, 2005, the first business day after the due date of Sunday, August 14, 2005, along with a petition for extension of time, and is therefore timely filed. Although Applicants do not believe any additional fees are required, the Commissioner is authorized to charge any additional fees, including extension fees or other relief, which may be required, or credit any overpayment to Deposit Account No. 50-2319 (Our Order No. 465174-00312; Our Docket No.: A-68668).

I. REAL PARTY IN INTEREST

The real party in interest is The Regents of the University of California, owner by assignment of the present patent application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences which will directly affect, be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The present application was originally filed with claims 1-12. Claims 1-12 were cancelled in a preliminary amendment and claims 13-32 were added. In response to a Restriction Requirement, claims 21-25 and 27-31 were elected, and claims 13-20 were withdrawn. Claims 22, 25, 26, 20-30, and 32 have been cancelled. The claims on appeal, claims 21, 27, 28, and 31 as currently pending, are set forth in Appendix A.

IV. STATUS OF AMENDMENTS

No amendments to the claims have been made subsequent to the rejection of those claims herein.

V. SUMMARY OF INVENTION

The presently claimed invention is directed to methods for inhibiting the growth of non-T-cell tumor cells in a mammalian host. The methods comprise contacting at least one T cell of said host with (a) a self-antigen preparation comprising a cytokine-transduced irradiated tumor cell vaccine, and (b) a CTLA-4 blocking agent. Contacting at least one T cell is effective to break immune tolerance against said self antigen and stimulate an autoreactive T cell response against said tissue cells and inhibit growth of said non T cell tumor cells expressing said self antigen.

Self-antigens are described, for example, from page 19, line 8 through page 20, line 13. Self-antigens comprising cytokine-transduced tumor cells are described, for example, from page 47, line 12 through page 66, line 18.

CTLA-4 blocking agents that specifically bind to the extracellular domain of CTLA-4 and inhibit CTLA-4 signaling are described, for example, from page 8 – page 17. A CTLA-4

blocking agent comprising an antibody or a fragment thereof is described from page 11, line 27 – page 15, line 11.

VI. ISSUES

The Final Office Action dated October 8, 2004 included a number of issues now presented for appellate review:

A) Priority claim: The Patent Office incorrectly alleges that claim 21 lacks support in Provisional Application Ser. No. 60/110,761 and U.S. Patent Application No. 08/760,288.

B) 35 U.S.C. § 112, first paragraph: new matter: The Patent Office erroneously alleges that:

a) Claim 21 is not sufficiently supported by the priority documents and present disclosure for "non-T cell tumor cells"; and

b) Claim 21 is not sufficiently supported by the present disclosure for "self antigen expressed on tissue cells and non T cell tumor cells arising from said tissue."

C) 35 U.S.C. § 112, first paragraph: enablement: The Patent Office erroneously alleges that claims 21, 23-25, 27, 28, and 31 are not enabled.

D) 35 U.S.C. § 112 first paragraph: written description: The Patent Office erroneously alleges that claims 21, 23-25, 27, 28, and 31 lack proper written description for a) the phrase "wherein said CTLA-4 blocking agent comprises an antibody or a fragment thereof" and b) the phrase "tissue specific self antigens."

E) 35 U.S.C. § 102: The Patent Office erroneously alleges that claims 21, 23, 24, 27 and 31 are anticipated over:

1) Leach et al., Science 271:1734-1736 (1996)) as evidenced by van Elsas et al., J. Exp. Med. 190:355-366 (1999));

2) U.S. Patent No. 5,811,097 as evidenced by van Elsas and Lavesque et al.;

3) U.S. Patent No. 5,855,887 as evidenced by van Elsas and Lavesque et al.;

4) Hurwitz et al. Proc. Natl. Acad Sci. USA 95:10067-10071 (1998) as evidenced by van Elsas;

5) van Elsas et al., (J. Exp Med. 190:355-366 (1999); and

6) U.S. Patent No. 6,051,227 as evidenced by Lavesque et al., J. Clin. Lab. Anal. 9:123-128 (1995) and van Elsas et al.

F) 35 U.S.C. § 103: The Patent Office has erroneously alleged that claims 21 and 28 are obvious over van Elsas in view of U.S. Patent No. 6,051,227.

VII. GROUPING OF CLAIMS

Claims 21, 25, 27, 28, and 31 stand rejected. For purposes of appeal, claims 21, 25, 27, 28, and 31 are grouped together and stand or fall together.

VIII. ARGUMENTS

A. Applicant is entitled to the priority of 60/110,761 and 08/760,288

The Patent Office alleges that claim 21 lacks support in applications 60/110,761 and 08/760,288 for "non-T cell tumor cells." The Patent Office further alleges that application 08/760,288 does not provide support for a self antigen preparation comprising a tissue specific self antigen. The Examiner therefore erroneously concludes that the claimed subject matter is only entitled to an effective filing date of December 3, 1999.

1. Non-T cell tumor cells

Applications 60/110,761 and 08/760,288 both clearly provide sufficient descriptive support for the phrase "non-T cell tumor cells."

The standard for determining the sufficiency of a priority document is whether the written description of the document reasonably conveys to the person of ordinary skill in the art that applicant has possession of the invention. This standard does not require a claim to be described in *ipsis verbis*. See M.P.E.P. § 2163.01. As stated in the M.P.E.P.:

> If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d

> 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

M.P.E.P. § 2163 II A. 3(a). Moreover, mere rephrasing of descriptions in the disclosure is not new matter. See M.P.E.P. § 2163.07.

Applications 60/110,761 and 08/760,288 both provide clear written support for the exclusion of T cell tumor cells from the presently-claimed methods. Application 60/110,761 states at page 19, lines 24-26 that "administration of the subject blocking agents may be contra-indicated for certain lymphomas. In particular, T cell lymphomas may not benefit from increased activation." Application 08/760,288 states the same passage at page 18, lines 23-25. As is well known in the field, lymphomas refer to tumors of the lymphoid tissues, and diagnosis of T cell lymphomas typically occurs in the presence of a lymphoblastic cell, which is a T cell tumor cell. The term "contra-indicated" refers to the inadvisability or unsuitability of, *e.g.*, medical treatment, and the skilled artisan would readily recognize the potential downside to contacting a T cell tumor cell in a patient with an agent that could further stimulate it. The priority specifications provide an explicit suggestion and explanation of this exclusion, and the skilled artisan would fully recognize and understand the nature, scope and need for the "non-T cell tumor" claim limitation based on these teachings and particularly in light of the stated effects of the present invention. Based on these disclosures, one of skill in the art would inevitably conclude that applications 60/110,761 and 08/760,288 both support the claimed limitation to non-T cell tumor cells.

2. Self-antigen preparation comprising a tissue specific self antigen.

The Patent Office further contests support in 08/760,288 for a method comprising contacting at least one T cell of said host with a "self-antigen preparation comprising a tissue specific self antigen." Without acquiescing to the Examiner's rejection, and solely to expedite prosecution on the merits, Applicant has deleted the phrase "a tissue specific self-antigen," thus mooting the rejection.

As indicated above, there is ample support for the presently-claimed subject matter in both 60/110,761 and 08/760,288 and the instant case is therefore entitled to their respective priority dates of December 3, 1998 and December 4, 1996.

B. Rejection Under 35 U.S.C. § 112, first paragraph: new matter

Claims 21, 23-25, 27, 28, and 31 stand rejected under 35 U.S.C. § 112 first paragraph for allegedly adding new matter unsupported by the disclosure. Applicant respectfully traverses the rejection.

1. Non-T cell tumor cells are fully supported by the written description.

As a first basis for the rejection, the Examiner contends that claim 21 is not sufficiently supported by the priority documents and the present disclosure for "non-T cell tumor cells." Specifically, the Examiner is of the opinion that the present disclosure's reference to the administration of CTLA-4 blocking agents as being contraindicated for certain lymphomas, particularly T cell lymphomas, does not support the exclusion of treatment of "non-T cell tumors."

The Examiner has failed to make the requisite prima facie case for lack of written description. As stated above and reiterated here, the standard for determining sufficiency of written description is whether the disclosure reasonably conveys to the person of ordinary skill in the art the support at applicant has possession of the invention. This standard does not require a claim to be described in *ipsis verbis*. As stated in the MPEP § 2163 II A. 3(a):

> If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

Mere rephrasing of descriptions in the disclosure is not new matter. See MPEP § 2163.07.

The sufficiency of support is readily apparent to those of skill in the art. As discussed above, the specification expressly states that "administration of the subject blocking agents may be contra-indicated for certain lymphomas. In particular, T cell lymphomas may not benefit from increased activation." (Page 21, lines 7-9). Clearly, the skilled artisan would recognize that a method for stimulating T cells might be problematic for a patient suffering from a T cell lymphoma, *i.e.*, a patient having T cell tumor cells. The specification provides an explicit suggestion of and basis for this exclusion, which in all likelihood would be self-evident to the skilled artisan given the stated effects of the claimed invention on T cell stimulation. In any event, the skilled artisan would readily recognize that the claims are directed to a non-T cell tumor cell, and would certainly understand why such a limitation was

included as well as the attendant scope and parameters of such a limitation. One of skill in the art would clearly conclude that Applicant had possession of the claimed invention based on the explicit teachings provided in the specification and, accordingly, the rejection for lack of written description should be withdrawn.

2. Non T cell tumor cells "arising from said tissue."

As a second basis for the rejection, the Patent Office contests support for non T cell tumor cells "arising from said tissue." Although the Examiner admits that "the specification discloses 'a self antigen common to both normal and cancerous tissue can be targeted,'" the Examiner contends that "this disclosure fails to provide the necessary written support for the claim language, since the disclosure does not specify that the cancerous tissue arises [from] the normal tissue, which commonly expresses the self antigen."

As stated previously and reiterated here, without acquiescing to the Examiner's rejection, and solely to expedite prosecution on the merits, Applicant has deleted the phrase "arising from said tissue," thus mooting the rejection. Applicant therefore respectfully requests that this ground for rejection be withdrawn.

III. Rejections Under 35 U.S.C.§ 112, first paragraph: enablement

Claims 21, 23-25, 27, 28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph as being allegedly nonenabled. Applicant respectfully traverses.

In maintaining his rejection, the Examiner cites the previously-discussed references of Christadoss, Sullivan, Chambers, Anderson, and Yang for the alleged problems associated with CTLA-4. The Examiner further cites art references discussing the limitations of cancer vaccines in general. The Examiner accepts that the results in the Hodi and Phan references submitted by Applicant teach that CTLA-4 blockade 1) inhibits the growth of moderately immunogenic tumors and 2) in combination with cancer vaccines, increases rejection of poorly immunogenic tumors, thus acknowledging that CTLA-4 blockade indeed inhibits tumor cell growth. Despite this express acknowledgement of the efficacy of the presently-claimed methods, however, the Examiner nevertheless maintains his enablement rejection based on a number of perceived shortcomings that in the Examiner's opinion could allegedly impede clinical success. In doing so, the Examiner is clearly demanding much more from Applicant than is actually required under 35 U.S.C. § 112, first paragraph.

Specifically, in attempting to restrict the implications of the results in the submitted Hodi and Phan references to the scope of enablement, the Examiner cites the results in Hodi in which patients previously immunized with melanosomal antigens "evoked only less significant antitumor effects" as support for the perceived problem with the "unpredictability of whether the invention can be used *successfully* to inhibit growth of tumor cells." Office Action of July 8, 2004, page 6, first paragraph (Emphasis added). Apparently, the Examiner is imposing an enablement standard that requires not only a demonstration of human clinical utility by a patent applicant, but also "successful" human clinical utility as determined by the Examiner's own arbitrary standard. The patent law clearly maintains no such standard.

Applicant has already gone well beyond what is required in providing the Examiner with published follow-on human clinical data concerning the subject invention. Unfortunately, in focusing solely on the clinical outcomes for a fraction of these patients, all of whom are in the *late stages* of the disease, the Examiner ignores the stated positive outcomes in assessing enablement. Even the Examiner notes that 1) CA-125 antigen in ovarian cancer patients decreased, and 2) tumor necrosis occurred in melanoma patients. Thus, CTLA-4 treatment results in positive outcomes for two different types of cancers in a majority of the patients in the study. Yet this is ignored in formulating the rejection.

The Examiner appears to be holding Applicant to a standard having nothing to do with the enablement requirement. The Examiner accepts the results of Phan, which showed that treatment with CTLA-4 blockade and melanocyte antigen resulted in *clinical benefit for 21%* of Stage IV melanoma patients. As the Examiner is no doubt aware, Stage IV is the most advanced stage where the tumor has spread to other organs or to lymph nodes far away from the original tumor. The Examiner nevertheless dismisses the reference as demonstrative of enablement because some of the patients developed an autoimmune reaction, asserting that this side effect is a critical shortcoming that actually undercuts the enablement of the presently-claimed methods. Not only does this erroneously expand the legal requirements by improperly asserting that side effects are at all relevant in determining enablement; it ignores the requirement that the evidence must be viewed as a whole in determining enablement.

The dismissal of the results in Phan and the continued maintenance of the enablement rejection for the reasons cited in the rejection is directly contrary to the M.P.E.P. and to numerous Federal Circuit decisions regarding the issue of clinical safety and efficacy in determining enablement. See M.P.E.P. § 2164.05. Notably, the M.P.E.P. states:

> The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use in humans as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted.

See MPEP § 2107.03. Patentability, including the issue of enablement, does not require a showing that the treatment is safe. Nevertheless, Applicant presents Appendix B, "Researchers Shut Off Immune Cell Inhibition, Causing Tumor Shrinkage and Autoimmunity in Patients With Metastatic Melanoma," a June 23, 2003 article from the National Cancer Institute describing results using anti-CTLA-4 antibodies and gp100, showing that autoimmune side effects were treatable with steroids, but also suggesting that a necessary and acceptable consequence of the subject therapy is an autoimmune reaction, a concept clearly emphasized in the present disclosure. The safety of CTLA-4 blockade is also indicated in Appendix C: Keler, T. et al., "Activity and Safety of CTLA-4 Blockade Combined with Vaccines in Cynomolgus Macaques," *J. Immunol.* 171(11):6251-9 (2003)).

More significantly, the requirement of a clinical benefit is not the standard to judge patentability and enablement, let alone a "successful" clinical result in every instance. It is the language of the claims that controls the inquiry, which in this case require the inhibition of non-T cell tumor cell growth. This standard is clearly set forth in the case of In re Brana, where the Federal Circuit elaborated on the requirements under 112, ¶ 1 for pharmaceutical compounds. In Brana, the PTO and the Board of Patent Appeals had rejected a claim to a compound disclosed as having antitumor properties, in part, for lack of a showing that the compounds had predictive success in treating humans. The Federal Circuit, in reversing the decision of the Board, held that the PTO and the Board had confused the requirement of the law for obtaining a patent versus obtaining government approval for marketing a drug to treat humans:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. . . Authorization for a Phase II study means that the drug may be administered to a large number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the *safety of the drug* when administered to a larger human population, as well as *its potential efficacy under different dosage regimens.* FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of

> patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

In sum, the Patent Office has substituted its own non-legal standard for the correct legal standard of enablement. All of the evidence presented by Applicant clearly supports the enablement of the presently-claimed methods. Indeed, the use of CTLA-4 blockade for treating various tumors is in clinical trials, with positive outcomes seen in many patients even with a single dose of an anti-CTLA-4 antibody. Further, and in any event, human clinical data is not a prerequisite to receiving a patent. Successful inhibition of non-T cell tumor cell growth has already been shown in numerous art-accepted murine models in the instant specification. This is all that the patent law requires. By applying a standard of a "successful" clinical outcome for every human patient, the standard applied by the Patent Office grossly exceeds that required to show enablement of the full scope of the claims. Overwhelming evidence supports enablement of the inhibition of tumor cell growth as presently claimed. The Patent Office has clearly failed to establish a case of *prima facie* case of non-enablement, and Applicant therefore respectfully requests that this ground for rejection be withdrawn.

IV Rejections Under 35 U.S.C. § 112 first paragraph: written description

Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph for alleged inadequate written description. Applicant respectfully traverses this rejection.

1. CTLA-4 blocking agent comprising an antibody or fragment thereof

The rejection alleges that the phrase "wherein said CTLA-4 blocking agent comprises an antibody or a fragment thereof" would include CTLA-4 blocking agents other than an antibody. The Patent Office interpretation, however, is contrary to a construction that would be given under the Written Description Guidelines and also contradictory to basic canons of claim construction.

First, the claim is direct to a genus of antibodies with CTLA-4 blocking agent activity. The Written Description Guidelines pointed to by the Examiner are clearly contrary to the Examiner's position. For example, Applicants direct the Examiner to Example 8, illustrating a claim of the following scope: "An isolated and purified nucleic acid *comprising* SEQ ID NO:2." The analysis provided by the PTO construes the claim as being directed to a genus of nucleic acids that minimally contains SEQ ID NO:2 and not a genus of nucleic acids generally. Analogously, Claim 21 is directed to use of a CTLA-4 blocking agent for inhibiting tumor cell growth, where the CTLA-4 blocking agent comprises an antibody or fragment thereof. Thus, the claim is directed to the use of a *genus of antibodies* that bind to the extracellular domain of CTLA-4 and inhibit CTLA-4 signaling, and not a genus of CTLA-4 blocking agents. Consequently, the appropriate question for determining satisfaction of the written description requirement in the present case, as in Example 8 of the Written Description Guidelines, is *whether the genus of antibodies* useful as CTLA-4 blocking agent are adequately supported by the disclosure. It is undisputed that antibodies functioning as CTLA-4 blocking agent are fully supported. If the Examiner has any doubts as to Applicant's position regarding sufficiency for the genus of antibodies, Example 16 in the Written Description Guidelines should lay the matter to rest.

The strained construction given by the Examiner is also contrary to the basic canon of claim construction that it is improper to read a limitation from the specification into the claims. See MPEP ; see also E-Pass Techs., Inc. v. 3Com Corp., 67 USPQ2d 1947 (Fed. Cir. 2003) (Limitations appearing in the specification but not recited in the claim are not read into the claim). The claimed method defines precisely the nature of the CTLA-4 blocking agent as an antibody or fragment thereof, and by a construction that in essence *inserts an additional CTLA-4 blocking agent*, the Patent Office has changed the nature of the claim. Applicant has precisely defined the claimed invention in all its limitations and it is unreasonable to construe it in a manner different from the plain language of its terms. The term "comprising" allows additional unrecited elements with respect to the CTLA-4 blocking agent comprising antibodies and fragments thereof and not whether CTLA-4 blocking agent is other than an antibody or fragment thereof. Applicant submits that the rationale advanced to support the written description rejection is based on an improper construction of the claim. Withdrawal of the rejection is respectfully requested.

2. Tissue Specific Self-Antigens

Claims 21, 23-35, 27, 28, and 31 stand rejected for an allegedly inadequate written description with respect to "tissue specific" self antigens. The Examiner admits that "the specification describes some 'tissue specific' self antigens" at page 20, lines 1-7, but argues that "none of the exemplified self antigens are actually tissue specific" because they are expressed in other tissues. As discussed previously, without acquiescing or admitting to the Examiner's position, and solely to expedite prosecution on the merits, the claims have been amended to delete the referenced phrase, thus mooting the rejection. Applicant therefore respectfully requests withdrawal of the rejection.

V Rejections Under 35 U.S.C. § 102

A. Rejection of Claims 21, 23, 27, and 31 over Leach in view of van Elsas

Claims 21, 23, 27, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Leach et al., *Science* 271:1734-1736 (1996)) as evidenced by van Elsas et al., *J. Exp. Med.* 190:355-366 (1999)). Applicant respectfully traverses.

Without acquiescing or admitting to the Examiner's position, and solely to expedite prosecution on the merits, claim 21 has been amended to incorporate the limitations of claims 23 and 24. Since the Examiner did not reject claim 24 over Leach as evidenced by van Elsas, this ground for rejection is now moot. Applicant respectfully requests that it be withdrawn.

B. U.S. Patent No. 5,811,097 as evidenced by van Elsas and Lavesque et al.

Applicant traverses this ground for rejection.

C. U.S. Patent No. 5,855,887 as evidenced by van Elsas and Lavesque et al.

Applicant traverses this ground for rejection.

D. Rejections of claims 21, 23, 24, 27 and 31 as being anticipated by Hurwitz et al., van Elsas et al., and U.S. Patent No. 6,051,227 as evidenced by van Elsas

Claims 21, 23, 24, 27 and 31 stand rejected under 102(b) as being anticipated by Hurwitz et al. Proc. Natl. Acad Sci. USA 95:10067-10071 (1998) as evidenced by van Elsas. Applicant respectfully traverses.

As discussed in the response to the priority claim and new matter rejections above, the amended claims are fully supported by applications 60/110,761 and 08/760,288. Therefore, the cited reference is not prior art under any provision of 35 U.S.C. § 102.

Applicant therefore respectfully requests that this ground for rejection be withdrawn.

E. Rejections of claims 21, 23, 24, 27 and 31 under 35 U.S.C. 102(a) as being anticipated by van Elsas et al., (J. Exp Med. 190:355-366 (1999)

Claims 21, 23, 24, 27 and 31 stand rejected under 35 U.S.C. 102(a) as being anticipated by van Elsas et al., (J. Exp Med. 190:355-366 (1999). Applicant respectfully traverses.

As discussed in the response to the priority claim and new matter rejections above, the amended claims are fully supported by applications 60/110,761 and 08/760,288. Therefore, the cited reference is not prior art under any provision of 35 U.S.C. § 102.

Applicant therefore respectfully requests that this ground for rejection be withdrawn.

F. Rejections of claims 21, 23, 24, 27 and 31 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,051,227 as evidenced by Lavesque et al., J. Clin. Lab. Anal. 9:123-128 (1995) and van Elsas et al.

Claims 21, 23-25, 27, 28 and 31 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,051,227 as evidenced by Lavesque et al., J. Clin. Lab. Anal. 9:123-128 (1995) and van Elsas et al. Applicant respectfully traverses.

As discussed in the response to the priority claim and new matter rejections above, the amended claims are fully supported by applications 60/110,761 and 08/760,288. Therefore, the cited reference is not prior art under any provision of 35 U.S.C. § 102.

Applicant therefore respectfully requests that this ground for rejection be withdrawn.

VI Rejections Under 35 U.S.C. 103

Claims 21 and 28 stand rejected under 35 U.S.C. § 103(a) as being obvious over van Elsas in view of U.S. Patent No. 6,051,227. Applicant respectfully traverses the rejection.

As discussed in the response to the priority claim and new matter rejections above, the claims are fully supported by 60/110,761 and 08/760,288. van Elsas is therefore not prior art

under any provision of 35 U.S.C. § 102. The rejection under 35 U.S.C. § 103 is therefore improper, and Applicant respectfully request that this ground for rejection be withdrawn.

CONCLUSION

Based on the foregoing, Applicants respectfully request allowance of the pending claims.

Respectfully submitted,
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Dated: August 15, 2005

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CLAIMS APPENDIX

This listing of claims will replace all prior versions and listing of claims in the application.

1-12 (Cancelled)

13. (Withdrawn) A method for stimulating an immune response to a self antigen, said method comprising contacting a mammalian T cell with a first immune response stimulating agent and an effective dose of a CTLA-4 blocking agent characterized as specifically binding to the extracellular domain of CTLA-4 and inhibitory of CTLA-4 signaling;

wherein said dose is effective to increase the response of said mammalian T cell to said self antigen.

14. (Withdrawn) The method of Claim 13, wherein said first immune response stimulating agent comprises a self antigen preparation.

15. (Withdrawn) The method of Claim 14, wherein said self antigen preparation comprises a tumor vaccine comprising irradiated tumor cells.

16. (Withdrawn) The method of Claim 15, wherein said irradiated tumor cells comprise cytokine-transduced tumor cells.

17. (Withdrawn) The method of Claim 14, wherein said self antigen preparation comprises tumor cell lysates.

18. (Withdrawn) The method of Claim 14, wherein said self antigen preparation comprises purified protein.

19. (Withdrawn) The method of Claim 13, wherein said mammalian T cell, said first immune response stimulating agent and said CTLA-4 blocking agent are further combined with a second immune response stimulating agent either simultaneously or sequentially.

20. (Withdrawn) The method of Claim 13, wherein said mammalian T cell is an autoreactive mammalian T cell.

21. (Currently Amended) A method for inhibiting the growth of non-T-cell tumor cells in a mammalian host, the method comprising:

contacting at least one T cell of said host with (a) a self antigen preparation comprising cytokine transduced tumor cells ~~a tissue specific self antigen, wherein said self antigen is expressed on tissue cells and non-T cell tumor cells arising from said tissue~~ and (b) a CTLA-4 blocking agent characterized as specifically binding to the extracellular domain of CTLA-4 and inhibitory of CTLA-4 signaling, wherein said CTLA-4 blocking agent comprises an antibody or a fragment thereof,

wherein said contacting is effective to break immune tolerance against said self antigen and stimulate an autoreactive T cell response against said tissue cells and inhibit growth of said non T cell tumor cells expressing said self antigen.

22. (Cancelled)

23. (Cancelled)

24. (Cancelled)

25. (Cancelled)

26. (Cancelled)

27 (Previously presented) The method of Claim 21, wherein said contacting step comprises administering said self antigen preparation and said CTLA-4 blocking agent to said mammalian host either simultaneously or sequentially.

28. (Previously presented) The method of Claim 21, wherein said contacting step occurs *ex vivo* and said at least one T cell is administered to said host.

29. (Cancelled)

30. (Cancelled)

31. (Previously presented) The method of Claim 21, comprising contacting said mammalian T cell with an immune response stimulating agent either simultaneously or sequentially.

32. (Cancelled)